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Chronic Toxicity of Lead and Cadmium I. Changes in the Central Nervous System of the Parental Generation of Rats After Chronic Intoxication with Lead and Cadmium

Slaska Akademia Medyczna
Katowice (Poland)

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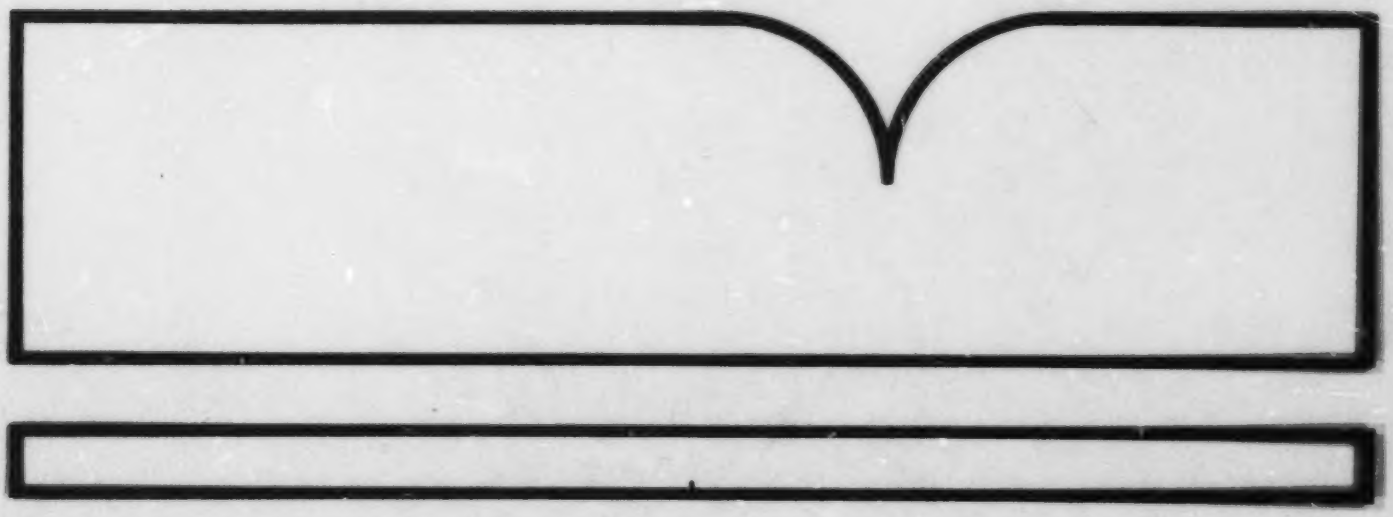

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16. ABSTRACT

This paper examines the effects of chronic exposure to trace amounts of lead and cadmium on the central nervous system of male Westar rats. Treatments consisted of two levels of lead (5 or 50 ppm), two levels of cadmium (0.1 or 5 ppm), and two combined dosages (5 ppm lead and 0.1 ppm cadmium, or 50 ppm lead and 5 ppm cadmium). Treatments were administered in buffered drinking water.

The lower dosages generally produced hyperactivity, while higher dosages produced hypoactivity. Effects of lead and cadmium on biogenic amines varied with dose and area of the brain. Biochemical analysis of blood and urine showed no changes in the hematocrit or hemoglobin, but the activity of Delta-ALA dehydratase and serum phosphatase were differentially affected. Concentrations of lead and cadmium in the liver and kidney increased, and positive interaction effects were noted.

The results suggest that the level of biogenic amines in discrete brain areas is a very sensitive indicator of central nervous system toxicity to lead and/or cadmium.

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I. Changes in the Central Nervous System of the Parental Generation of Rats After Chronic Intoxication With Lead and Cadmium

By

Zbigniew. S. Herman, Krystyna Kmieciak-Kolada, Ryszard Szkilnik,
Ryszard Brus, Kornel Ludyga, Romana Winter, Jan Jonek,
Janusz Konecki, Jan Kusz, Jakub Bodziony,
Barbara Hebrowska, Kazimierz Kaminski,
Marie Ostrowska, Janwiga Wyrebowska,
and John Laskey

Departments of Pharmacology, Biochemistry
Cytology and Histology
Central Animal Farm of Silesian Medical Academy
in Katowice

Project Officer

John Laskey
Health Effects Research Laboratory
U.S. Environmental Protection Agency
Research Triangle Park, NC 27711

HEALTH EFFECTS RESEARCH LABORATORY
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY

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ABSTRACT

This paper examines the effects of chronic exposure to trace amounts of lead and cadmium on the central nervous system of male Wistar rats. Treatments consisted of two levels of lead (5 or 50 ppm), two levels of cadmium (0.1 or 5 ppm), and two combined dosages (5 ppm lead and 0.1 ppm cadmium, or 50 ppm lead and 5 ppm cadmium). Treatments were administered in buffered drinking water.

The lower dosages generally produced hyperactivity, while higher dosages produced hypoactivity. Effects of lead and cadmium on biogenic amines varied with dose and area of the brain. Biochemical analysis of blood and urine showed no changes in the hematocrit or hemoglobin, but the activity of Delta-ALA dehydratase and serum phosphatase were differentially affected. Concentrations of lead and cadmium in the liver and kidney increased, and positive interaction effects were noted.

The results suggest that the level of biogenic amines in discrete brain areas is a very sensitive indicator of central nervous system toxicity to lead and/or cadmium.

SECTION 1

INTRODUCTION

Coal is a major source of energy in the USA and Poland. During processing, the hazardous trace elements contiguous with coal ore, such as lead (Pb) and cadmium (Cd), may be transferred to rivers and drinking water sources resulting in chronic human exposure. In recent years, the Pb and Cd content in the environment and in man has increased progressively (12,13,14,15,16,20). In 1971, the annual averages of Cd_3 concentration in air from ten cities in Poland ranged from 0.002 to 0.05 $\mu g/m^3$ (16). The brain, reproductive system and other organ systems may be targets for the potentially toxic effects of these elements (14,17,18,19). Taking into account the possible individual and synergistic effects of chronic exposure to Pb and/or Cd, it seemed practical to study the functional physiology of the central nervous and reproductive systems in rats chronically exposed to trace amounts of Pb and/or Cd in the drinking water.

In this paper we report the influence of these elements on the central nervous system.

SECTION 2

MATERIALS AND METHODS

Experiments were carried out on male Wistar rats, 40 days old, from the Central Animal Farm of the Silesian Academy of Medicine. With the exception of the control group which contained 40 animals, the animals were divided into groups consisting of 20 rats each and received via drinking water (buffered with 0.005 M acetate) the following treatments.

Group I (Control)

Group II - 5 ppm lead

Group III - 50 ppm lead

Group IV - 0.1 ppm cadmium

Group V - 5 ppm cadmium

Group VI - 5 ppm lead and 0.1 ppm cadmium

Group VII - 50 ppm lead and 5 ppm cadmium

Behavioral Measurements

Because of the large numbers of animals to be tested, 24 hour locomotor activity was assessed in two waves. Wave I consisted of a control, 5 ppm Pb, 0.1 ppm Cd and 5 ppm Pb plus 0.1 ppm Cd; and Wave II consisted of control, 50 ppm Pb, 5 ppm Cd and 50 ppm Pb plus 5 ppm Cd. Rats were placed for 24 hours in a photocell actometer (1) and for the next 24 hours in a motimeter (2). They had access to standard laboratory feed and water for 1/2 hour following 6, 12 and 24 hours in each measuring device for the length of the experiment. Impulses elicited by locomotor activity were noted from counters every 12 hours.

Biogenic Amine Assays

Rats were killed by cervical dislocation at the end of experiments. The brains were quickly removed and placed on Petri dishes filled with

ice and dissected into the hypothalamus, medulla oblongata plus pons, hippocampus with nucleus accumbens and striatum essentially according to Glowinski and Iversen (3). Spectrophotofluorometric analysis of noradrenaline (NA), 5-hydroxytryptamine (5-HT), and 5-hydroxyindoleacetic acid (5-HIAA) levels were done according to Miller et al. (4) and dopamine (DA) according to Cox et al. (5).

Biochemical Studies

Blood samples were collected by heart puncture into heparinized syringes under light ether anesthesia. The brain was perfused through the subclavian and carotid arteries with 60 ml of saline cooled to 4°C. The brain was removed and immediately frozen in dry ice, weighed and homogenized in 5 parts of 0.067 M sodium phosphate buffer, pH 7.4 in a teflon homogenizer and placed in a beaker filled with ice. Blood levels of hemoglobin (6) and δ-aminolevulinic acid dehydratase E.C.4.2.1.24 (ALA-D) (7) were measured. Lactate dehydrogenase E.C.1.1.1.27 (LDH) activity was measured spectrophotometrically, alkaline phosphatase E.C.3.1.3.1 (Al.Ph.) activity was estimated according to Bessey et al. (3), brain acetycholinesterase E.C.3.1.1.7 (AChE) activity was measured according to Ellman et al. (9), and brain monoamine oxidase E.C.1.4.3.4. (MAO) activity was measured according to McEven and Cohen (10) using benzylamine as a substrate. The level of coproporphyrin in the urine was estimated according to Haeger-Aronsen (11). Lead and cadmium concentrations in 1 gram aliquots of liver, kidney and drinking water were determined on a Pye-Unicain SP90A Series 2 atomic absorption spectrophotometer.

SECTION 3

RESULTS

Locomotor Activity

Continuous (40 days) exposure to Pb and/or Cd (5 ppm Pb or 5 ppm Pb plus 0.1 ppm Cd) produced hyperactivity when measured in the photocell apparatus or in the motimeter (Table 1). The 0.1 ppm Cd exposure group, however, was hyperactive in the photocell apparatus and hypoactive in the motimeter. Animals exposed to higher levels of Pb and/or Cd (50 ppm Pb, 5 ppm Cd or 50 ppm Pb and 5 ppm Cd) were hypoactive in both measuring devices. Ratios of diurnal-nocturnal activity did not show consistent dose-related changes.

Neurochemical Analyses

NA and DA concentrations in brain areas are presented in Tables 2 and 3. Chronic exposure to 5 ppm Pb did not change the NA concentrations in the brain areas examined, but a decrease in DA concentrations in the striatum were noted. Cd at 0.1 ppm decreased the level of NA in all brain areas except the striatum, but lowered DA level in this area. After simultaneous exposure to Pb and Cd (5 ppm Pb and 0.1 ppm Cd) only a decrease in the NA level in hypothalamus was observed.

Pb at 50 ppm in the water resulted in a decrease in the NA concentration in all areas except the limbic system (hippocampus with nucleus accumbens) and lowered DA levels in the striatum. Cd at 5 ppm increased NA concentration in the hypothalamus. After exposure to 50 ppm Pb + 5 ppm Cd, there was an increase in NA concentration in the hypothalamus and a decrease in DA concentration in the striatum.

5-HT and 5-HIAA concentrations in brain areas are presented in Tables 4 and 5. Lead at 5 ppm resulted in increased concentration of both 5-HT and 5-HIAA in the hypothalamus. Cadmium at 0.1 ppm increased 5-HT concentrations in the brain stem and 5-HIAA concentrations in the hypothalamus and the striatum. Simultaneous administration of 5 ppm Pb + 0.1 ppm Cd increased the concentrations of both 5-HT and 5-HIAA in the brain stem, 5-HT levels in the limbic system and 5-HIAA concentrations in the hypothalamus and striatum.

Lead at 50 ppm decreased the 5-HT and 5-HIAA concentrations in the hypothalamus and striatum. Five ppm Cd decreased the concentration of 5-HT in the striatum. Simultaneous exposure to 50 ppm Pb and 5 ppm Cd decreased the concentrations of both of 5-HT and 5-HIAA in the hypothalamus and striatum.

TABLE 1. LOCOMOTOR ACTIVITY (COUNTS/24 HR) FOLLOWING 40 DAYS EXPOSURE TO Pb AND/OR Cd[a]

	Control	5 ppm Pb	0.1 ppm Cd	5 ppm Pb + 0.1 ppm Cd	SD_p[b]	ANOVA[c] P Value
Photocell Apparatus (Day 1)	322	717*[d]	696*	787*	83	<.01
Motimeter (Day 2)	349	433	201	395	51	<.05

	Control	50 ppm Pb	5 ppm Cd	50 ppm Pb + 5 ppm Cd	SD_p	ANOVA P Value
Photocell Apparatus (Day 1)	1172	723	972	476*	129	<.01
Motimeter (Day 2)	304	89**	156*	122*	32	<.01

a-N = 10 for each group.

b-SD_p = pooled standard deviation.

c-Significance level for the analysis of variance (ANOVA).

d-Values significantly different from control values by Dunnett's multiple comparison test (**p<.01, *p<.05).

TABLE 2. NORADRENALINE CONCENTRATION (µg/g) IN DISCRETE BRAIN AREAS FOLLOWING LEAD AND/OR CADMIUM EXPOSURE[a]

Brain area	Control	Pb 5 ppm	Cd 0.1 ppm	Pb 5 ppm + Cd 0.1 ppm	SD_p[b]	ANOVA[c] P Value
Hypothalamus	2.79	2.80	2.50	2.46	.28	<.05
Pons with Medulla Oblongata	0.78	0.79	0.66**[d]	0.73	.06	<.01
Hippocampus with Nucleus Accombens	0.55	0.54	0.47	0.51	.28	N.S.
Striatum	0.20	0.24	0.21	0.22	.09	N.S.
	Control	Pb 50 ppm	Cd 5 ppm	Pb 50 ppm + Cd 0.1 ppm	SD_p[b]	ANOVA[c] P Value
Hypothalamus	2.71	1.62**	5.83**	5.83**	.44	<.01
Pons with Medulla Oblongata	0.76	0.68	0.80	0.71	.06	<.01
Hippocapmus with Nucleus Accombens	0.77	0.75	0.69	0.71	.13	N.S.
Striatum	0.20	0.13	0.19	0.19	.09	N.S.

a-N - 10 for each group.

b-SD_p = pooled standard deviation.

c-Significance level from the analysis of variance (ANOVA).

d-Values significantly different from control values by Dunnett's multiple comparison test (**p<.01).

TABLE 3. DOPAMINE CONCENTRATION (μg/g) IN STRIATUM FOLLOWING LEAD AND/OR CADMIUM EXPOSURE[a]

Control	Pb 5 ppm	Cd 0.1 ppm	Pb 5 ppm + Cd 0.1 ppm	SD_p[b]	ANOVA[c] P Value
7.13	6.05	4.79*[d]	5.85	1.74	<.01
Control	Pb 50 ppm	Cd 5 ppm	Pb 50 ppm + CD 5 ppm	SD_p[b]	ANOVA P Value
9.27	6.39*	10.68	7.51	2.34	<.01

a-N = 10 for each group.

b-SD_p = pooled standard deviation.

c-Significance level from the analysis of variance (ANOVA).

d-Values significantly different from control values by Dunnett's multiple comparison test (*p<.05).

Biochemical Analyses

No significant changes in hematocrit of hemoglobin were noted in animals on any exposure regimen. Delta-ALA dehydratase activity in erythrocytes was significantly decreased by exposure to 50 ppm Pb, 50 ppm Pb plus 5 ppm Cd, and 5 ppm Pb plus 0.1 ppm Cd but not by exposure to 5 ppm Pb. Neither serum AChE nor serum LDH were altered by any treatment. Serum alkaline phosphatase activity was increased by treatment with 0.1 ppm Cd, 5 ppm Cd and 50 ppm Pb plus 5 ppm Cd.

Brain MAO activity was reduced by both Cd treatments and Pb-Cd treatments, however, only the 5 ppm Pb treatment caused reduced activity (Table 6). Brain AChE activity was significantly reduced by 50 ppm Pb and 50 ppm Pb-5 ppm Cd combination (Table 6).

Twenty-four hour urinary coproporphyrin was unaffected by the low doses of Pb and/or Cd treatment but decreased more than 50% by 50 ppm Pb and increased more than 250% by the 50 ppm Pb-5 ppm Cd combination.

Concentration of Pb and Cd in Tissues

Cadmium and Pb concentrations in the liver and kidney are presented in Table 7. It should be noted that the Pb treated animals when simultaneously treated with Cd showed increased liver and kidney Pb concentrations over that resulting from Pb treatment alone. Likewise, when Cd treated animals are simultaneously treated with Pb, liver and kidney Cd concentrations are higher than with Cd treatment alone. No measurable quantities of Pb or Cd were found in the drinking water.

TABLE 4. 5-HYDROXYTRYPTAMINE CONCENTRATIONS (μg/g) IN DISCRETE BRAIN AREAS FOLLOWING LEAD AND/OR CADMIUM EXPOSURE[a]

Brain area	Control	Pb 5 ppm	Cd 0.1 ppm	Pb 5 ppm + Cd 0.1 ppm	SD_p[b]	ANOVA[c] P Value
Hypothalamus	2.50	3.01**[d]	2.59	2.54	.28	<.01
Pons with Medulla Oblongata	1.04	1.08	1.25**	1.30**	.09	<.01
Hippocampus with Nucleus Accombens	0.61	0.61	0.67	0.68	.32	N.S.
Striatum	1.07	1.00	1.02	1.18	.32	N.S.
	Control	Pb 50 ppm	Cd 5 ppm	Pb 50 ppm + Cd 5 ppm	SD_p[b]	ANOVA[c] P Value
Hypothalamus	2.72	1.95	2.73	2.04**	.32	<.01
Pons with Medulla Oblongata	1.03	0.98	1.11	1.04	.13	N.S.
Hippocapmus with Nucleus Accombens	0.99	0.99	1.03	0.98	.09	N.S.
Striatum	1.09	0.70**	0.83*	0.86	.19	<.01

a-N - 10 for each group.

b-SD_p = pooled standard deviation.

c-Significance level from the analysis of variance (ANOVA).

d-Values significantly different from control values by Dunnett's multiple comparison test (**p<.01, *p<.05).

TABLE 5. 5-HYDROXYINDOLEACETIC ACID CONCENTRATION (μg/g) IN DISCRETE BRAIN AREAS FOLLOWING LEAD AND/OR CADMIUM EXPOSURE[a]

Brain area	Control	Pb 5 ppm	Cd 0.1 ppm	Pb 5 ppm + Cd 0.1 ppm	SD_p[b]	ANOVA[c] P Value
Hypothalamus	2.27	2.88**[d]	2.85*	2.69*	.35	<.05
Pons with Medulla Oblongata	0.70	0.73	0.64	0.83	.32	N.S.
Hippocampus with Nucleus Accombens	0.99	1.08	1.06	1.00	.25	N.S.
Striatum	0.98	0.94	1.12	1.37	.44	N.S.
	Control	Pb 50 ppm	Cd 5 ppm	Pb 50 ppm + Cd 5 ppm	SD_p[b]	ANOVA[c] P Value
Hypothalamus	2.33	1.75**	1.87**	1.47**	.28	<.01
Pons with Medulla Oblongata	0.72	0.74	0.88	0.76	.09	N.S.
Hippocapmus with Nucleus Accombens	0.61	0.65	0.79	0.78	.13	N.S.
Striatum	0.98	0.77	0.82	0.69	.44	N.S.

a-N - 10 for each group.

b-SD_p = pooled standard deviation.

c-Significance level from the analysis of variance (ANOVA).

d-Values significantly different from control values by Dunnett's multiple comparison test (**p<.01, *p<.05).

TABLE 6. MONAMINE OXIDASE AND ACETYLCHOLINE ESTERASE (μg/min/g) CONCENTRATIONS IN WHOLE BRAIN FOLLOWING LEAD AND/OR CADMIUM EXPOSURE[a]

Analysis	Control	Pb 5 ppm	Cd 0.1 ppm	Pb 5 ppm + Cd 0.1 ppm	SD_p[b]	ANOVA[c] P Value
Monoamine Oxidase	1.49	0.70	0.51	1.00	1.14	N.S.
	Control	Pb 50 ppm	Cd 5 ppm	Pb 5 ppm + Cd 5 ppm	SD_p	ANOVA P Value
	1.61	1.57	0.76	0.33	1.55	N.S.
	Control	Pb 5 ppm	Cd 0.1 ppm	Pb 5 ppm + Cd 0.1 ppm	SD_p[b]	ANOVA[c] P Value
Acetylcholine Esterase	10.3	9.1	10.7	10.4	2.86	N.S.
	Control	Pb 50 ppm	Cd 5 ppm	Pb 50 ppm + Cd 5 ppm	SD_p	ANOVA P Value
	12.0	4.2**[d]	10.4	8.7*	2.66	<.01

a-N - 10 for each group.

b-SD_p = pooled standard deviation.

c-Significance level from the analysis of variance (ANOVA).

d-Values significantly different from control values by Dunnett's multiple comparison test (**p<.01, *p<.05).

TABLE 7. LIVER AND KIDNEY LEAD OR CADMIUM CONCENTRATIONS FOLLOWING 40 DAYS EXPOSURE[a]

	5 ppm Pb	5 ppm Pb + 0.1 ppm Cd	50 ppm Pb	50 ppm Pb + 5 ppm Cd
Liver Pb Concentration, µg/g	2.3 ± 0.2	2.7 ± 0.3[b]	2.7 ± 0.3[b]	3.2 ± 0.5[b]
Kidney Pb Concentration, µg/g	2.1 ± 0.3	2.4 ± 0.3	2.3 ± 0.2	2.7 ± 0.4[b]
	0.1 ppm Cd	0.1 ppm Cd + 5 ppm Pb	5 ppm Cd	5 ppm Cd + 50 ppm Pb
Liver Cd Concentration, µg/g	0.52 ± 0.10	0.59 ± 0.08	0.63 ± 0.18	0.68 ± 0.11[b]
Kidney Cd Concentration, µg/g	0.59 ± 0.05	0.80 ± 0.07[b]	0.75 ± 0.11[b]	0.95 ± 0.23[b]

a-N for each group = 10.

b-Significantly different from the low dose by Dunnett's multiple comparison test ($p<0.05$).

SECTION 4

DISCUSSION

These results indicate that chronic exposure to 50 ppm Pb and 5 ppm Cd for 40 days in drinking water to young rats is deleterious to CNS function. Higher concentrations of Pb generally lowered both NA and DA concentrations in brain areas measured. Exposure to 5 ppm Pb increased the concentration of 5-HT in the hypothalamus, and the concomitant treatment of the 5 ppm Pb group with 0.1 ppm Cd had the same effect in the brain stem. Inversely it seem that treatment with 50 ppm Pb decreased 5-HT in the hypothalamus and striatum. The higher Cd exposure level depressed the 5-HT concentration in the striatum.

These results indicate that estimation of the level of biogenic amine levels in discrete brain areas is a very sensitive indicator of CNS toxicity to Pb and/or Cd. Both agents have a different profile of action on adrenergic and serotoninergic neurons in the discrete brain areas measured in this study. No relationship between the levels of biogenic amines and MAO activity was seen. The decrease of AChE activity observed in animals exposed to high Pb levels may be interpreted as an influence of this metal on cholinergic neurons. Shih and Hanin (24), in a study with rats exposed from infancy to 4% lead acetate in chow, showed a decrease in acetylcholine concentrations in cortex, hippocampus, midbrain and striatum by 35, 54, 51 and 33%, respectively. This finding provides evidence for an inhibitory effect of Pb on the central cholinergic function in vivo. There is some experimental evidence that biogenic amines in the CNS act by the adenylcyclase-3'5'cyclic AMP system (27,28,29,30,31). Very low concentrations of Pb or Cd inhibited adenylate cyclase activity in homogenates and particulate fractions of rat cerebellum and cerebral cortex. On the other hand, Pb stimulated and Cd inhibited phosphodiesterase activity (25).

Our results indicate that both heavy metals penetrated the brain. It was stated by others (26) that Pb penetrates the brain and is concentrated in cortical grey matter and basal ganglia whereas Cd does not readily penetrate the brain. All of these effects appear to be species dependent. Biochemical examinations carried out in our experiments have shown some typical signs of Pb and Cd intoxication. They also indicate that LDH and AChE activity in serum have no value as a diagnostic factor in Pb and Cd intoxication in rats. A dose dependent increase in serum alakaline phosphatase activity was seen with Cd treatment. The significance of this will be confirmed in studies currently in progress. Our data suggest that a brief Pb and/or Cd exposure affects the subtle functions of the CNS. The toxicological importance of these changes requires further elucidation.

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